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Homeostasis with Multiple Inputs*

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Abstract. Homeostasis is a regulatory mechanism whereby some output variables of a system are kept approximately constant as input parameters vary over some region. Important applications include biological and chemical systems. In [M. Golubitsky and I. Stewart, *J. Math. Biol.*, 74 (2017), pp. 387–407], we reformulated homeostasis in the context of singularity theory by replacing "approximately constant over an interval" by "zero derivative with respect to the input at a point" and discussed coordinate changes that put the singularity in normal form. We call this form of homeostasis *infinitesimal homeostasis*. Reed et al. [*Bull. Math. Biol.*, 79 (2017), pp. 1–24] show by example that biologically relevant biochemical mechanisms can exhibit homeostasis even though infinitesimal homeostasis does not occur for realistic model parameters.) The main focus in [M. Golubitsky and I. Stewart, *J. Math. Biol.*, 74 (2017), pp. 387–407] was on systems with one input and one output variable, classified by a subfamily of the elementary catastrophes of Thom [*Structural Stability and Morphogenesis*, Benjamin, Reading MA, 1975] and Zeeman [*Catastrophe Theory: Selected Papers* 1972–1977, Addison-Wesley, London, 1977]. In this paper, we use the singularity theory approach to study simultaneous homeostasis for two input parameters. As before, coordinate changes that preserve homeostasis play a prominent role because such coordinate changes provide the basis for singularity theory. We classify the singularities concerned and discuss their effect on homeostasis. We also speculate on why homeostasis in models may look as though it comes from infinitesimal homeostasis. This speculation uses the classification of elementary catastrophes and discusses why certain singularities (chairs and hyperbolic umbilics) may be expected to occur as a system evolves towards homeostasis.

Key words. homeostasis, singularity theory, catastrophe theory, biochemical networks

AMS subject classifications. 92B99, 34C99, 34K18

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1. Introduction and outline.

1.1. Homeostasis. Many biological systems regulate physiological variables that are important for the survival of the organism by keeping them approximately constant in a varying environment. This is an example of *homeostasis*, a concept that goes back to Claude Bernard [3] in 1865; the name was introduced by Cannon [7]. For example, thermoregulation in mammals maintains approximately constant body temperature despite large changes in external temperature [12, 13, 22]. The "input-output function" mapping external temperature to body temperature is relatively flat over a significant interval of external temperatures. Figure 1 shows experimental input-output data using these variables for the brown opossum

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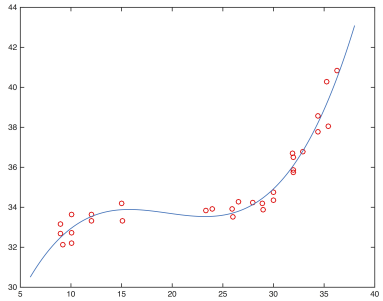

Figure 1. *Experimental data (circles) from* [17, 18] *showing thermoregulatory homeostasis in the brown opossum and fitted cubic input-output function (curve). The horizontal axis is* environmental temperature *(°C), and the vertical axis is* body temperature *(°C).*

together with a fitted cubic input-output function. Nijhout et al. [18] call this shape of an input-output function $Z(\lambda)$ a *chair*. According to [18], the chair metaphor has both a region of *homeostasis* where a quantity is approximately constant, called the *plateau*, and regions of *escape from homeostasis* where that quantity varies linearly away from homeostasis.

In [10], we identify a chair with the *fold catastrophe* $Z(\lambda) = \lambda^3$ and show that we can search for chairs by finding parameter values λ_0 where the input-output function satisfies $Z'(\lambda_0) = Z''(\lambda_0) = 0$ and $Z'''(\lambda_0) > 0$. Biologically relevant examples of chair searches using singularity theory are given in Reed et al. [20] and Antoneli et al. [1]. Using universal unfolding theory, we have also shown [10] that any small perturbation of a chair has a similar region of homeostasis (plateau) to the chair singularity itself. Specifically, the plateau is located at approximately the same parameter values, and invariants such as asymptotic growth rates as parameters vary are preserved.

Biological homeostasis is often based, wholly or partly, on a network of biochemical reactions. Homeostasis in the regulation of blood glucose concentration by insulin, where insulin levels may have to change substantially in order to keep blood sugar constant, is such an example. Ma et al. [15] identify, among all three-node enzyme networks with Michelis–Menten chemical kinetics, two networks that are able to *adapt*, that is, to reset themselves after responding to an external stimulus. Further examples include regulation of cell number and size [14]; regulation of blood pH, water content, and oxygen content [5]; and the control of sleep [24]. The literature is huge, and these articles are a random sample. The term "homeostasis" is also used more widely, for example, in ecology, chemistry, and control engineering.

Other kinds of homeostasis occur when one variable is held approximately constant on variation of two or more input parameters. For example, body temperature can be homeostatic with respect to both external temperature *and* amount of exercise. A biological network example is homeostasis of extracellular dopamine (eDA) in response to variation in the activities of the enzyme tyrosine hydroxylase (TH) and the dopamine transporters (DAT) (Best et al. [4]). These authors derive a differential equation model for the biochemical network of Figure 2 (left). They fix reasonable values for all parameters in the model with the exception of the concentrations of TH and DAT. Figure 2 (right) shows the equilibrium value of eDA as a function of TH and DAT in their model. The white dots indicate the predicted eDA values for the observationally determined values of TH and DAT in the wild-type genotype

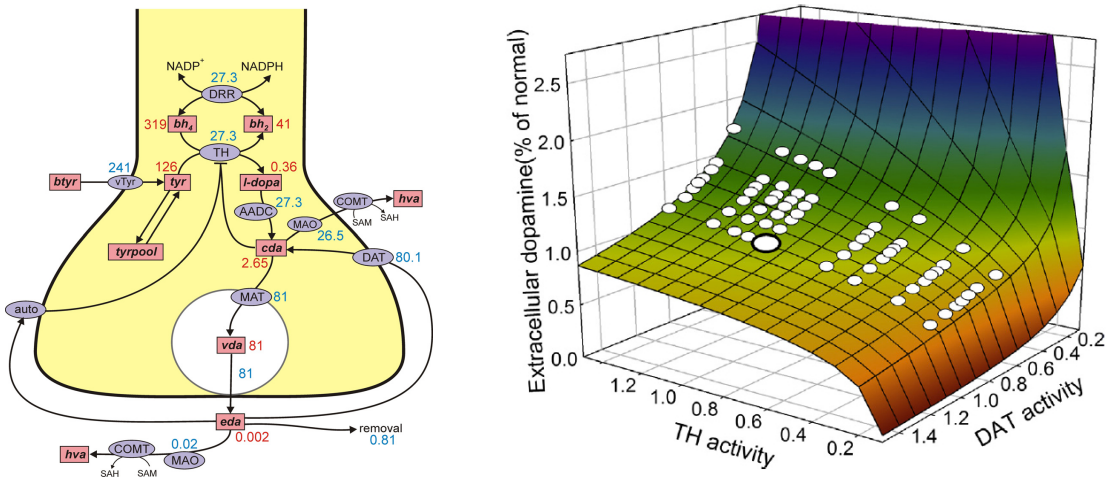

Figure 2. *(Left): Biochemical network for dopamine synthesis, release, and reuptake in Nijhout et al. [4]. (Right): Figure 8 of Nijhout et al. [18]. At equilibrium there is homeostasis of eDA as a function of TH and DAT. There is a plateau around the wild-type genotype (large white disk). Smaller disks indicate positions of polymorphisms of TH and DAT found in human populations.*

(large white disk) and the polymorphisms observed in human populations (small white disks). Their result is scientifically important because almost all of the white disks lie on the plateau (the region where the surface is almost horizontal) that indicates homeostasis of eDA. Note that the flat region contains a line from left to right at about eDA = 0.9. In this respect, the surface graph in Figure 2 (right) appears to resemble that of a nonsingular perturbed hyperbolic umbilic (see Table 1) in Figure 3. See also the level contours of the hyperbolic umbilic in Figure 4. This figure shows that the hyperbolic umbilic is the only low-codimension singularity that contains a single line in its zero set.

Mathematical models of these systems often use ODEs and thus have common features that make it possible to formulate a general version of homeostasis that applies to many different examples. In [10], we developed a singularity theory approach for homeostasis where one internal variable is approximately constant on variation of one input parameter. Here we focus on the case where one internal variable is approximately constant on variation of multiple input parameters. Specifically, we consider the singularity theory details when there

Table 1

Classification of singularities of input-output maps $\mathbb{R}^2 \to \mathbb{R}$ of codimension ≤ 3.

Name	Normal form	Codim	Universal unfolding
Morse (simple homeostasis)	$\pm\lambda_1^2 \pm \lambda_2^2$	0	$\pm\lambda_1^2 \pm \lambda_2^2$
fold (chair)	$\lambda_1^3 \pm \lambda_2^2$	1	$\lambda_1^3 + a\lambda_1 \pm \lambda_2^2$
cusp	$\pm\lambda_1^4 \pm \lambda_2^2$	2	$\pm\lambda_1^4 + a\lambda_1^2 + b\lambda_1 \pm \lambda_2^2$
swallowtail	$\lambda_1^5 \pm \lambda_2^2$	3	$\lambda_1^5 + a\lambda_1^3 + b\lambda_1^2 + c\lambda_1 \pm \lambda_2^2$
hyperbolic umbilic	$\lambda_1^3 + \lambda_2^3$	3	$\lambda_1^3 + \lambda_2^3 + a\lambda_1\lambda_2 + b\lambda_1 + c\lambda_2$
elliptic umbilic	$\lambda_1^3 - 3\lambda_1\lambda_2^2$	3	$\lambda_1^3 - 3\lambda_1\lambda_2^2 + a(\lambda_1^2 + \lambda_2^2) + b\lambda_1 + c\lambda_2$

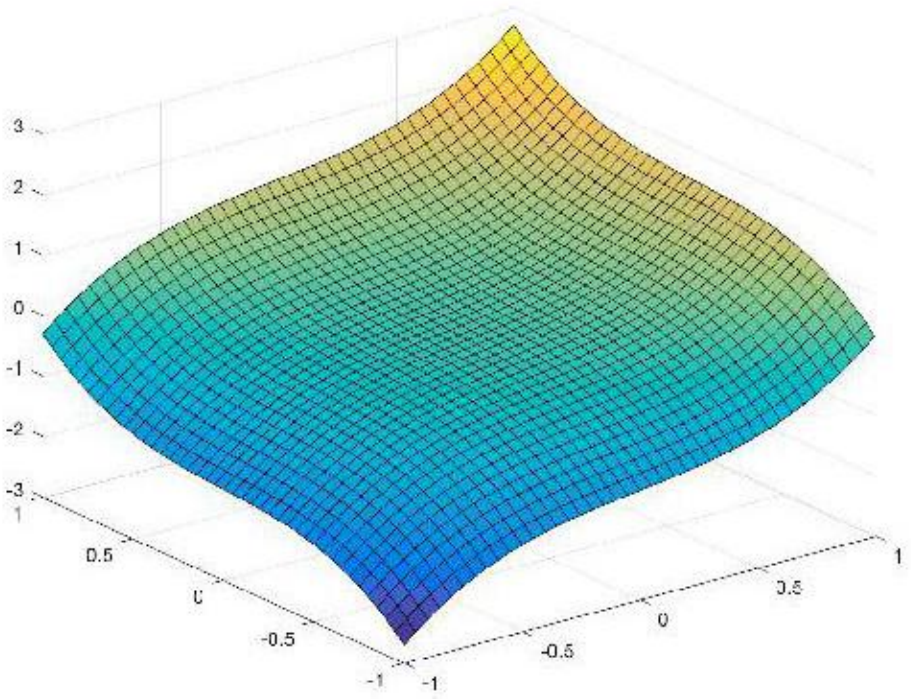

Figure 3. *Graph of surface of perturbed hyperbolic umbilic without singularities:* $Z(\lambda_1, \lambda_2) = \lambda_1^3 + \lambda_2^3 + \lambda_1 + \lambda_2/2$.

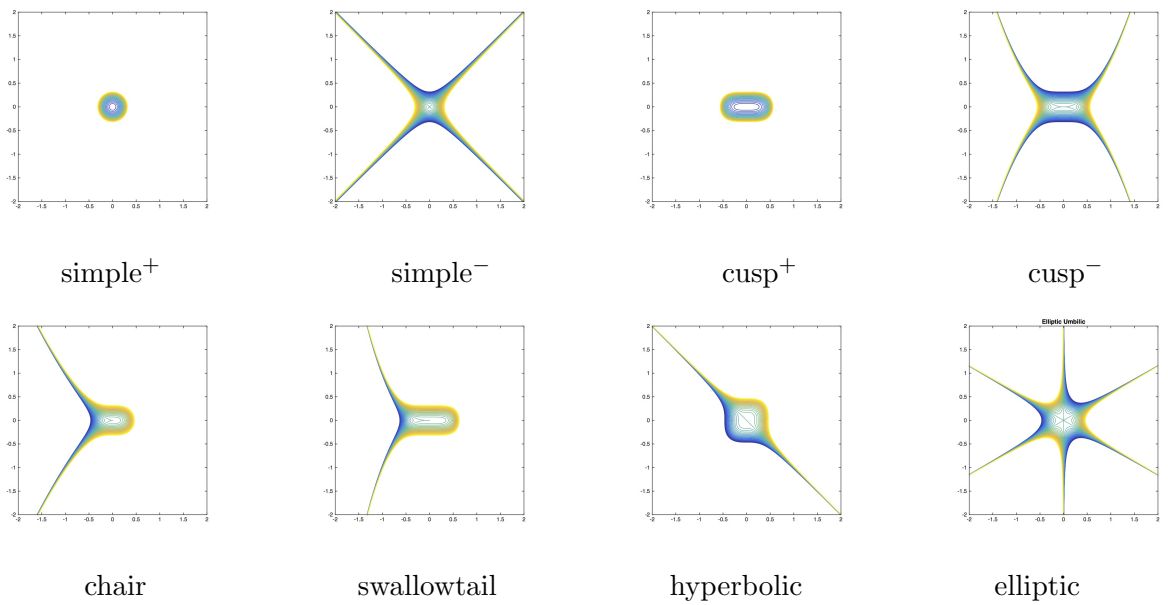

Figure 4. *Plateaus consisting of contour plots for each singularity in Table 1. Yellow boundary indicates decrease from plateau, and blue boundary indicates increase from plateau.*

are two input parameters. This approach distinguishes two main types of variable: *external parameters* and *internal variables*, which are further divided into two types: *controlled* and *manipulated*. These are standard terms in the biological literature, related to control-theoretic models. We mention manipulated variables because they are present in models, but our focus is on the resulting behavior of the controlled variables. The manipulated variables play a role in the dynamics because the model creates homeostasis in the controlled variable by changing the manipulated variables in a way that roughly cancels the effects of the external parameters.

In a model ODE, the inputs play the role of parameters, whose values affect the dynamics of the system. Homeostasis occurs when there is some region in input-parameter space for which the controlled state variable is approximately constant. The manipulated variables can behave in any manner whatsoever and play no significant role in a singularity-theoretic analysis, which effectively eliminates them.

1.2. Outline of paper. In section 2, we define input-output functions, following the special case discussed in [9]. We define homeostasis of one output relative to several inputs using a general "infinitesimal" definition of homeostasis (Definition 2.2).

In Lemma 3.1, we introduce changes of coordinates on input-output functions that preserve homeostasis. These changes of cooordinates are precisely those that are used in the classification of elementary catastrophes (Table 1). Here the codimension of a singularity is a measure of its complexity, equal to the number of parameters required to generate all topological types of perturbations [6, 8, 19, 25]. Table 2 in this section also lists defining conditions for the elementary catastrophes, which can be used to find such singularities in model equations.

Figure 4 of section 4 shows the shapes of plateaus (regions of homeostasis) near each of the low-codimension singularities. The plateau has simple features that distinguish the different singularities, such as asymptotic growth rates of aspects of its shape, and the geometry and number of "whiskers" that may extend for relatively large distances. We do not formalize

Table 2

Decision tree for recognizing normal forms of singularities of input-output maps $Z : \mathbb{R}^2 \to \mathbb{R}$ of codimension ≤ 3. All derivatives in the table are evaluated at z^0. Δ = discriminant of $Z_{\lambda\lambda\lambda}$ as a cubic form; u = null-vector of $Z_{\lambda\lambda}$; v = eigenvector of $Z_{\lambda\lambda}$ for nonzero eigenvalue. Subscripts in u, v denote directional derivatives.

Rank ($Z_{\lambda\lambda}$)	Normal form	Conditions ($Z_\lambda = 0$ throughout)
2	$\pm\lambda_1^2 \pm \lambda_2^2$	$\det Z_{\lambda\lambda} \neq 0$, $\pm$ given by signs of eigenvalues of $Z_{\lambda\lambda}$
1	$\lambda_1^3 + \lambda_2^2$	$Z_{uu} = 0, Z_{uuu} \neq 0; Z_{vv} > 0$
1	$\lambda_1^3 - \lambda_2^2$	$Z_{uu} = 0, Z_{uuu} \neq 0; Z_{vv} < 0$
1	$\lambda_1^4 + \lambda_2^2$	$Z_{uu} = Z_{uuu} = 0, Z_{uuuu} > 0; Z_{vv} > 0$
1	$\lambda_1^4 - \lambda_2^2$	$Z_{uu} = Z_{uuu} = 0, Z_{uuuu} > 0; Z_{vv} < 0$
1	$-\lambda_1^4 + \lambda_2^2$	$Z_{uu} = Z_{uuu} = 0, Z_{uuuu} < 0; Z_{vv} > 0$
1	$-\lambda_1^4 - \lambda_2^2$	$Z_{uu} = Z_{uuu} = 0, Z_{uuuu} < 0; Z_{vv} < 0$
1	$\lambda_1^5 + \lambda_2^2$	$Z_{uu} = Z_{uuu} = Z_{uuuu} = 0, Z_{uuuuu} \neq 0; Z_{vv} > 0$
1	$\lambda_1^5 - \lambda_2^2$	$Z_{uu} = Z_{uuu} = Z_{uuuu} = 0, Z_{uuuuu} \neq 0; Z_{vv} < 0$
0	$\lambda_1^3 + \lambda_2^3$	$Z_{\lambda\lambda} = 0, \Delta < 0$
0	$\lambda_1^3 - 3\lambda_1\lambda_2^2$	$Z_{\lambda\lambda} = 0, \Delta > 0$

these notions here (although this can be done). The aim is just to point out that they exist and that they distinguish the singularities.

In particular the similarity between the plateau region corresponding to Figure 2 (right) and the plateau region in the hyperbolic umbilic is noted. As proof of concept, an example of a two-input infinitesimal chair occurring in a biochemical network is given in section 5, and its presence is deduced from the recognition conditions for the appropriate singularity. This example is based on the description of the feed-forward excitation motif given in [20].

Section 6 examines why chairs and hyperbolic umbilics are perhaps the two most likely singularities in input-ouput functions with one output. The paper ends with a brief sketch of the analogous setup for multioutput homeostasis and the role of networks in homeostasis.

2. Input-output map.

In general terms, consider a parametrized family of ODEs

$$\dot{x} = F(x, \alpha), \tag{2.1}$$

where $x \in \mathbb{R}^n$ and $\alpha \in \mathbb{R}^p$. The *system variables* x can be spilt into *output variables* $z \in \mathbb{R}^\ell$ and the other variables $y \in \mathbb{R}^{n-\ell}$ (often called *manipulated variables*). The parameters $\alpha \in \mathbb{R}^p$ can also be split into *input parameters* $\lambda \in \mathbb{R}^k$ and *unfolding* or other system parameters $\beta \in \mathbb{R}^{p-k}$. We study how z depends on λ, for fixed β, at equilibria of the ODE. For notational convenience, we omit β from now on.

Suppose $x^0 = (y^0, z^0) \in \mathbb{R}^n = \mathbb{R}^{n-\ell} \times \mathbb{R}^\ell$ is a stable equilibrium of (2.1) at λ^0. (More generally, we could assume that x^0 is hyperbolic [11].) The equilibria of (2.1) are given by

$$F(x, \lambda) = 0. \tag{2.2}$$

By the implicit function theorem, we can solve (2.2) near (x^0, λ^0) to obtain a map $X : \mathbb{R}^k \to \mathbb{R}^n$ such that

$$F(X(\lambda), \lambda) \equiv 0, \tag{2.3}$$

where $X(\lambda_0) = x_0$. Let

$$X(\lambda) = (Y(\lambda), Z(\lambda))$$

be the projections of X onto the y, z coordinates.

Definition 2.1. *The* input-output map *of* (2.2) *near* (x^0, λ^0) *is* $Z : \mathbb{R}^k \to \mathbb{R}^\ell$.

Definition 2.2. *The point* (x^0, λ^0) *is an* infinitesimal homeostasis point *of* Z *if the derivative*

$$D_\lambda Z(x^0, \lambda^0) = 0. \tag{2.4}$$

In particular, (x^0, λ^0) *is a singularity—that is, the derivative of* Z *is singular there—but the vanishing of* all *first derivatives selects a special subclass of singularities, said to have "full corank."*

The interpretation of a homeostasis point is that the values of the z-variables determined by $Z(\lambda)$ differ from $Z(\lambda^0)$ in a manner that depends quadratically (or to higher order) on $\|\lambda - \lambda^0\|$. This makes the graph of $Z(\lambda)$ flatter than any growth rate with a nonzero linear term.

This condition is the motivation for requiring condition (2.4) rather than merely $D_\lambda Z(x^0, \lambda^0)$ being singular. The latter corresponds to homeostasis relative to some subspace of input variables, and in practice a model based explicitly on variables from that subspace would probably be more appropriate.

Remark 2.3. It is typical in homeostasis that the quantity that is held approximately constant, as the input λ varies is just one coordinate of the equilibrium, but this need not always be the case. For simplicity, assume $\ell = 1$. Then homeostasis can refer to a function of the equilibrium coordinates $\zeta : \mathbb{R}^n \to \mathbb{R}$ (often called an *observable*) being held approximately constant; that is,

$$Z(\lambda) = \zeta(X(\lambda))$$

is approximately constant. Of course, $\zeta = 0$ shows that the observable ζ needs to satisfy some genericity conditions to be relevant. We assume that $\frac{\partial \zeta}{\partial X_m}$ is nowhere zero when ζ depends on X_m. In particular, this condition is valid for any coordinate function $\zeta(X) = X_m$.

Definition 2.2 places the study of homeostasis in the context of singularity theory, and we follow the standard line of development in that subject. A detailed discussion of singularity theory would be too extensive for this paper. A brief summary is given in [10] in the context of homeostasis, accessible descriptions can be found in [19, 25], and full technical details are in [8, 16] and many other sources.

The singularity-theoretic approach involves the following steps:

- Define a class of coordinate changes that preserve homeostasis.
- Use these to *classify* singularities into equivalence classes and normal forms.
- Solve the *recognition problem* for each normal form; that is, state conditions on the Taylor series expansion of $Z(\lambda)$ that make it equivalent to the normal form concerned.
- Calculate the *universal unfolding* of the singularity, which organizes all small perturbations of $Z(\lambda)$ into a single family with a finite number of parameters.
- Deduce useful information from the normal form and its universal unfolding.

Following Nijhout et al. [18], we define the following:

Definition 2.4. *A* plateau *is a region of λ over which Z is approximately constant.*

As noted previously, the white disks in Figure 2 (right) fall mostly in the plateau of the graph of $Z(\mathrm{TH}, \mathrm{DAT})$.

Remark 2.5. Universal unfolding theory implies that small perturbations of Z (that is, variation of the suppressed parameters β) change the plateau region only slightly. This point was explored for the chair singularity in [10]. It follows that for sufficiently small perturbations, plateaus of singularities depend mainly on the singularity itself and not on its universal unfolding.

Remark 2.6. In section 6, we note that a system of equations that evolves toward (infinitesimal) homeostasis does so by transitioning through a singularity that has unfolding parameters with no infinitesimal homeostasis. It follows from this point of view that chair points, which are the simplest singularities with these kinds of perturbations, are likely candidates for transitions to homeostasis. See Theorems 6.2 and 6.3.

3. Catastrophe theory coordinate changes. Singularity theory applies in a wide range of mathematical contexts, and different kinds of coordinate change are appropriate in different circumstances. It is important to choose coordinate transformations that preserve the relevant structure in the application. As a pragmatic matter, coordinate changes that keep the computations as simple as possible are also preferred. Thus, the singularity-theoretic context must be chosen in a manner that is appropriate to the area of application.

We now show that in the present approach to homeostasis, there is a natural choice of coordinate transformations and that these turn out to be the standard coordinate changes used in elementary catastrophe theory. The proof is straightforward, but it is an essential step when setting up the method.

Lemma 3.1. *Let $\Lambda : \mathbb{R}^k \to \mathbb{R}^k$ be a diffeomorphism and $\kappa = (\kappa_y, \kappa_z)$ be a constant vector. Then transforming $F(x, \lambda)$ to*

$$\tilde{F}(x, \lambda) = F(x + \kappa, \Lambda(\lambda))$$

transforms the input-output function $Z(\lambda)$ to

$$\tilde{Z}(\lambda) = Z(\Lambda(\lambda)) - \kappa_z, \tag{3.1}$$

and homeostasis is preserved.

Proof. The graph of the zero set $X(\lambda)$ of (2.2) transforms to

$$\tilde{X}(\lambda) = X(\Lambda(\lambda)) - \kappa$$

since

$$\tilde{F}(\tilde{X}(\lambda), \lambda) = F(\tilde{X}(\lambda) + \kappa, \Lambda(\lambda)) = F(X(\Lambda(\lambda)) - \kappa + \kappa, \Lambda(\lambda)) = F(X(\Lambda(\lambda)), \Lambda(\lambda)) = 0.$$

Addition of a constant κ does not change the Jacobian with respect to x, so the transformed equilibria are also stable. Moreover, the input-output function $Z(\lambda)$ transforms to (3.1). Since adding a constant does not change a plateau region, the plateau region of Z transforms to the plateau region of $\tilde{Z}$ via the diffeomorphism Λ^{-1}. ∎

In other words, infinitesimal homeostasis points of an input-output function for a general dynamical system are classified by equivalences (3.1) of singularities of full corank. These changes of coordinates (arbitrary changes of coordinates in the domain $\Lambda(\lambda)$ and addition of a constant κ in the range) of $Z(\lambda)$ are precisely those used in elementary catastrophe theory [19, 25] and hence those used to prove the normal form and unfolding theorems listed in this paper. See the discussion in section 7, where the coordinate change issue is an obstacle to developing a multioutput infinitesimal homeostasis theory.

Remark 3.2. For a more general input-output map $Z(\lambda) = \zeta(X(\lambda))$ defined in Remark 2.3, we can still change coordinates by $\lambda \mapsto \Lambda(\lambda)$ and add a constant κ, that is,

$$Z(\lambda) \mapsto Z(\Lambda(\lambda)) + \kappa.$$

Here the addition of the constant κ is justified because we are looking for plateaus on which Z is approximately constant but not specifically what that constant is.

Remark 3.3. In this paper, we focus on how singularities in the input-output map shape plateaus, and we use the normal form and unfolding theorems of elementary catastrophe theory to do this. We remark that typically the variables other than Z, the manipulated variables Y, can vary substantially while the ouput variable is held approximately constant. See, for example, Figure 3 in [1].

Intuitively, the output variables remain approximately constant *because* the manipulated variables can change significantly. The two types of variable are linked together because the entire system is in equilibrium. However, in singularity-theoretic terms, the manipulated variables correspond to the directions in which the mapping is regular rather than singular. Their mathematical effect on the type of singularity is therefore trivial.

3.1. Catastrophe theory classification. When $\ell = 1$, the results of [10] reduce the classification of homeostasis points for a single node to that of singularities of input-output maps $\mathbb{R}^k \to \mathbb{R}$. This is precisely the abstract setup for elementary catastrophe theory [6, 8, 19, 25].

When $k = 1$, the case discussed in [10], the singularity is determined by the first nonvanishing λ-derivative $Z^{(r)}(0)$ (unless all derivatives vanish, which is an "infinite codimension" phenomenon that we do not discuss further). If such an r exists, the normal form is $\pm\lambda^r$, where the sign can be made positive for odd r. When $r \geq 3$, the universal unfolding is

$$\pm\lambda^r + a_{r-2}\lambda^{r-2} + a_{r-3}\lambda^{r-3} + \cdots + a_1\lambda$$

for parameters a_j. When $r = 2$, the universal unfolding is $\pm\lambda^2$. The codimension in this setting is $r - 2$. See Example 14.9 and Theorem 15.1 in [6], Chapter IV (4.6) and Chapter VI (6.3) in [8], and [16] Chapter XI, section 1.1, and Chapter XII, sections 3.1 and 7.2 in [16].

We now consider $k = 2$. Table 1 summarizes the classification when $k = 2$, so $\lambda = (\lambda_1, \lambda_2) \in \mathbb{R}^2$. Here the list is restricted to codimension ≤ 3. The associated geometry, especially for universal unfoldings, is described in [6, 8, 19] up to codimension 4. Singularities of much higher codimension have also been classified, but the complexities increase considerably. For example, Arnold [2] provides an extensive classification up to codimension 10 for the complex analogue, functions $\mathbb{C}^n \to \mathbb{C}$.

Remark 3.4. Because $k = 2$, the normal forms for $k = 1$ appear again, but now there is an extra quadratic term $\pm\lambda_2^2$. This term is a consequence of the splitting lemma in singularity theory, arising here when the second derivative $\mathrm{D}^2 Z$ has rank 1 rather than rank 0 (corank 1 rather than corank 2). See [6, 19, 25]. The presence of the $\pm\lambda_2^2$ term affects the range over which $Z(\lambda)$ changes when λ_2 varies but not when λ_1 varies.

3.2. Recognition conditions. Given an input-output map $Z : \mathbb{R}^2 \to \mathbb{R}$ and taking coordinates $(\lambda_1, \lambda_2) \in \mathbb{R}^2$ and a point z^0, we characterize the corresponding normal form in Table 1 for singularities of codimension ≤ 3. The relevant normal form depends on the low-order terms in the Taylor series of $Z(\lambda)$.

The decision tree involved is summarized in Table 2. All derivatives in the table are evaluated at λ^0.

4. Normal forms and plateaus. The standard geometric features considered in catastrophe theory focus on the gradient of the function $Z(\lambda)$ in normal form. In contrast, what

matters here is the function itself. Specifically, we are interested in the region in the λ-plane where the function Z is approximately constant.

More specifically, for each normal form $Z(\lambda)$, we choose a small $\delta > 0$ and form the set

$$P_\delta = \{\lambda \in \mathbb{R}^2 : |Z(\lambda)| \leq \delta\}. \tag{4.1}$$

This is the plateau region on which $Z(\lambda)$ is approximately constant, where δ specifies how good the approximation is. If $Z(\lambda)$ is perturbed slightly, P_δ varies continuously. Therefore, we can compute the approximate plateau by focusing on the singularity rather than on its universal unfolding.

This observation is important because the universal unfolding has many zeros of the gradient of $Z(\lambda)$, hence "homeostasis points" near which the value of $Z(\lambda)$ varies more slowly than linear. However, this structure seems less important when considering the relationship of infinitesimal homeostasis with homeostasis. See the discussion of the unfolding of the chair summarized in [10, Figure 3].

The "qualitative" geometry of the plateau—that is, its differential topology and associated invariants—is characteristic of the singularity. This offers one way to infer the probable type of singularity from numerical data; it also provides information about the region in which the system concerned is behaving homeostatically. We do not develop a formal list of invariants here, but we indicate a few possibilities.

The main features of the plateaus associated with the six normal forms are illustrated in Table 1. Figure 4 plots, for each normal form, a sequence of contours from $-\delta$ to δ; the union is a picture of the plateaus. The color indicates the contour value with yellow for $-\delta$ and blue for δ. By unfolding theory, these features are preserved by small perturbations of the model and by the choice of δ in (4.1) provided it is sufficiently small. Graphical plots of such perturbations (not shown) confirm this assertion. Again, we do not attempt to make these statements precise in this paper.

The number of curves ("whiskers") forming the zero-level contour of the plateau is a characteristic of the plateau. For example, Figure 2 appears to have one line in the plateau. This leads us to conjecture that the hyperbolic umbilic is the singularity that organizes the homeostatic region of eDA in the example discussed in [4]. It may be the case, however, that there is no infinitesimal homeostasis in this example and that the cause is more global. We discuss in section 6 why the chair and the hyperbolic umbilic are the singularities that might be expected to organize two output homeostasis.

5. An example of a two-input infinitesimal chair. As proof of concept, we show that the recognition conditions in Table 2 can be used to prove the existence of a double homeostasis point in a biochemical network modeling feed-forward excitation. In fact, we detect the presence of a two-input chair, with normal form $\lambda_1^3 + \lambda_2^2$. The model is deliberately chosen to be amenable to analytic calculation. As remarked in [1], with an example, numerical methods can be used to apply the same techniques to more complicated (and more "realistic") models.

As noted in [20], feed-forward excitation occurs in a biochemical network when a substrate activates the enzyme that removes a product, as depicted in Figure 5. In this motif, X, Y, Z are chemical substrates whose concentrations are denoted by x, y, z. Each straight arrow represents a flux coming into or going away from a substrate. The differential equations for

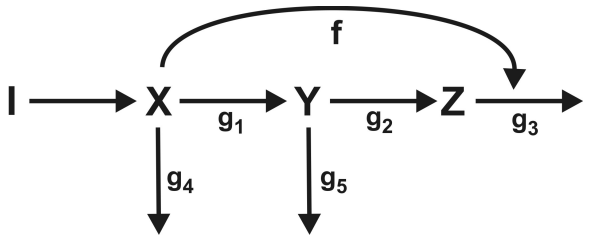

Figure 5. *The feed-forward excitation motif. The substrate X activates the enzyme that catabolizes Z.*

each substrate simply say that the rate of change of the concentration is the sum of the arrows going towards substrate minus the arrows going away.

The differential equations are

$$\begin{aligned} \dot{x} &= I - g_1(x) - g_4(x) \\ \dot{y} &= g_1(x) - g_2(y) - g_5(y) \\ \dot{z} &= g_2(y) - h(x,z), \end{aligned} \tag{5.1}$$

where $h(x,z)$ is often assumed to have the form $f(x)g_3(z)$. Feed-forward excitation is represented by

$$\frac{\partial h}{\partial x} > 0 \quad \text{and} \quad \frac{\partial h}{\partial z} > 0. \tag{5.2}$$

Theorem 5.1 ([20]). *Infinitesimal homeostasis of z with respect to I occurs at I_0 if and only if*

$$h_x(x_0,z_0) = \frac{g_1' g_2'}{g_2' + g_5'}, \tag{5.3}$$

where $(x_0,y_0,z_0) = (x(I_0),y(I_0),z(I_0))$ and the g_i' are evaluated at x_0, y_0, or z_0 as appropriate. An infinitesinmal chair occurs at I_0 if and only if (5.3) and

$$h_{xx}(x_0,z_0) = \frac{1}{g_2' + g_5'}\left(g_1'' g_2' + (g_1')^2 \frac{g_2'' g_5' - g_2' g_5''}{(g_2' + g_5')^2}\right) \tag{5.4}$$

are valid.

5.1. Double homeostasis when g_2 depends on a. When g_2 depends on a, the feed-forward excitation motif equations have the form

$$\begin{aligned} \dot{x} &= F(x) + I \quad &\equiv \quad & I - g_1(x) - g_4(x) \\ \dot{y} &= G(x,y,a) \quad &\equiv \quad & g_1(x) - g_2(y,a) - g_5(y) \\ \dot{z} &= H(x,y,z,a) \quad &\equiv \quad & g_2(y,a) - h(x,z), \end{aligned} \tag{5.5}$$

where I and a are considered as inputs.

Proposition 5.2. *A two-input chair in (5.5), for z with respect to (I,a), occurs at points where (5.3), (5.4), and*

$$g_{2,a}(y_0,a_0) = 0 \tag{5.6}$$

are valid.

Proof. Given Theorem 5.1, we need only consider implicit differentiation with respect to the second input a. Implicit differentiation of the first equation in (5.5) yields

$$F_x x_a = 0.$$

Since $F_x = -(g_{1,a} + g_{4,a}) \neq 0$, we obtain $x_a = 0$.

Implicit differentiation of the second and third equations in (5.5) yields

$$\begin{aligned} G_y y_a + G_a &= 0 \\ H_y y_a + H_z z_a + H_a &= 0 \end{aligned}$$

since $x_a = 0$. It follows that $z_a = 0$ if and only if

$$-H_y G_a + H_a G_y = 0.$$

However,

$$H_a G_y - H_y G_a = -g_{2,a}(g_2' + g_5') + g_2' g_{2,a} = -g_{2,a} g_5'.$$

So $z_a = 0$ if $g_{2,a} = 0$, as claimed in (5.6). ∎

Remark 5.3. A similar result is obtained by assuming that either g_1 or g_5 depends on a second input parameter a. The result is that infinitesimal homeostasis with respect to a occurs if either $g_{1,a} = 0$ or $g_{5,a} = 0$.

As an example, consider (5.1), where

$$g_1(x) = g_4(x) = g_3(x) = x \qquad g_2(y) = y \qquad g_5(y, a) = y - (a - 500)^2.$$

Also, assume $h(x, z) = f(x)g_3(z) = f(x)z$, where

$$f(x) = 1 + \frac{1}{1 + \exp\left(\frac{50 - x}{8.33}\right)}.$$

System (5.1) becomes

$$\begin{aligned} \dot{x} &= I - 2x \\ \dot{y} &= x - y - g_5(y, a) \\ \dot{z} &= y - f(x)z, \end{aligned} \tag{5.7}$$

where I and a are inputs. The zero set of (5.7) is

$$x = \frac{I}{2} \qquad y = \frac{I}{4} \qquad z = \frac{I/4}{f(I/2)}.$$

It follows from (5.3, 5.4) that an infinitesimal chair with respect to I occurs when

$$h_x(x, z) = f'(x)z = \frac{1}{2} \qquad \text{and} \qquad h_{xx} = f''(x)z = 0.$$

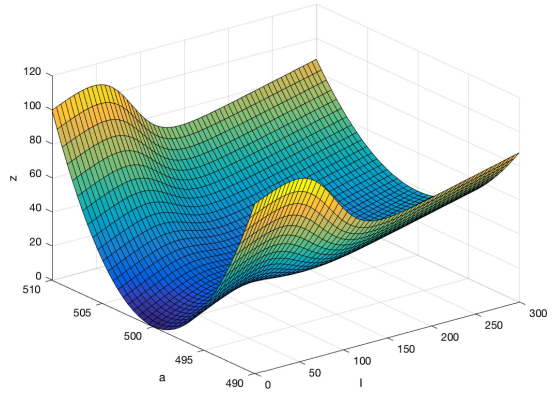

Figure 6. *Graph of surface of $z(I,a)$ in (5.8) that illustrates the two-dimensional chair.*

The zero set of (5.7) is

$$x(I) = I/2 \quad y(I,a) = I/4 + (a-500)^2 \qquad z(a,I) = y(I,a)/f(I/2). \tag{5.8}$$

Double homeostasis occurs when $a = 500$ and $I = 100$. To see this, observe that

$$g_{5,a} = 2(a-500) = 0,$$

that is, $a = 500$. Moreover, $h_{xx} = 0$ if and only if $f'' = 0$, which by direct calculation occurs when $x = 50$ and hence when $I = 100$. The graph of $z(x,I)$ (as defined in (5.8) and centered at $a = 500$ and $I = 100$) is shown in Figure 6. This illustrates the two-input chair, as expected.

6. Evolving towards homeostasis. Control-theoretic models of homeostasis often build in an explicit "target" value for the output and construct the equations to ensure that the input-output function is exactly flat over some interval. Such models are common and provide useful information for many purposes. In singularity theory, an exactly flat input-output function has "infinite codimension," so our approach is not appropriate for models of this type.

However, in biology, homeostasis is an emergent property of biochemical networks, not a preset target value, and the input-output function is only approximately flat, for example, as in Figure 1. Many of the more recent models of homeostasis do not assume a preset target value; instead, this emerges from the dynamics of a biochemical network. Here we expect typical singularities to have finite codimension, and our approach is then potentially useful. For example, in [10, section 8], we proved that for one such model of feed-forward inhibition [18, 21], the input-output map has a "chair" singularity, with normal form $x^3 + \lambda x$. Other examples of chair singularities are given in [20].

A key question is, in a mathematical sense, how does a biological system evolve towards homeostasis? Imagine a system of differential equations depending on parameters. Suppose that initially the parameters are set so that the associated input-output function has no regions of homeostasis. Now vary the parameters so that a small region of homeostasis appears in the input-output function. Since this region of homeostasis is small, we can assume that it is spawned by a singularity associated with infinitesimal homeostasis. How can that happen?

Singularities organizing evolution towards homeostasis. A plausible answer follows from the classification of elementary catastrophes. If there is one input and one output, the assumption of no initial homeostasis implies that $Z : \mathbb{R} \to \mathbb{R}$ is strictly increasing (or strictly decreasing). Generically, evolving towards infinitesimal homeostasis can occur in only one way. As a parameter β is varied, at some point λ^0 the input-ouput function $Z(\lambda)$ approaches a singularity, so there is a point λ^0 where $Z'(\lambda^0) = 0$. This process can happen only if $Z''(\lambda^0) = 0$ is also satisfied. That is, from a singularity-theoretic point of view, the simplest way that homeostasis can evolve is through an infinitesimal chair.

This process can be explained in the following way. The system can evolve towards infinitesimal homeostasis only if the universal unfolding of the singularity has a parameter region where the associated function is nonsingular. For example, simple homeostasis ($Z(\lambda) = \lambda^2$, which is structurally stable) does not have this property. All small perturbations of λ^2 have a Morse singularity. The simplest singularity that has nonsingular perturbations is the fold singularity$Z(\lambda) = \lambda^3$, that is, the infinitesimal chair.

At least two assumptions underlie this discussion. First, we have assumed that all perturbations of the input-output function can be realized by perturbations in the system of ODEs. This is true; see Lemma 6.1. Second, we assume that when evolving towards homeostasis, the small region of homeostasis that forms is one that could have grown from a point of infinitesimal homeostasis.

When Z depends on one parameter, generically the infinitesimal chair is the only possible singularity that can underlie the formation of homeostasis. In Theorem 6.3, we show that when $Z(\lambda)$ depends on two inputs, the lowest-codimension singularities having perturbations that are nonsingular are the chair and the hyperbolic umbilic. This discussion suggests that in systems with two input parameters, plateaus that form when evolving towards homeostasis should usually look like the plateau in the hyperbolic umbilic or the chair.

Lemma 6.1. *Given a system of ODEs $\dot{x} = F(x, \lambda)$ whose zero set is defined by*

$$F(X(\lambda), \lambda) \equiv 0$$

and a perturbation $\tilde{X}(\lambda) = X(\lambda) + P(\lambda)$ of that zero set, $\tilde{X}$ is the zero set of the perturbation

$$\tilde{F}(x, \lambda) = F(x - P(\lambda), \lambda).$$

Therefore, any perturbation of the input-output function $Z(\lambda)$ can be realized by perturbation of F.

Proof. Clearly,

$$\begin{aligned}\tilde{F}(\tilde{X}(\lambda), \lambda) &= \tilde{F}(X(\lambda) + P(\lambda), \lambda)\\ &= F(X(\lambda) + P(\lambda) - P(\lambda), \lambda)\\ &= F(X(\lambda), \lambda)\\ &= 0.\end{aligned}$$

If we write $P(\lambda) = (0, P_z(\lambda))$, where $P_z(\lambda)$ is a small perturbation of $Z(\lambda)$, then we can obtain the perturbation $Z + P_z$ of Z by the associated perturbation of F. ∎

Theorem 6.2. *Consider input-output functions with one input and one output. Then the only singularities of codimension ≤ 3 that have perturbations with no infinitesimal homeostasis are the fold (chair) and the swallowtail.*

Proof. It is easy to see that perturbations of λ^k always have a local minimum when k is even. So the only normal forms with perturbations that have no infinitesimal homeostasis occur when k is odd. Those that have codimension at most 3 are the fold ($k = 3$) and the swallowtail ($k = 5$). ∎

We remark that folds occur in the unfoldings of swallowtails and that the generic nonhomeostatic approach to a swallowtail would also give a nonhomeostatic approach to a fold (or chair).

Theorem 6.3. *Consider input-output functions with two inputs and one output. Then the only singularities of codimension ≤ 3 that have perturbations with no infinitesimal homeostasis are the fold (chair), swallowtail, and hyperbolic umbilic.*

Proof. Recall that for a two-input one-output input-output function $Z(\lambda_1, \lambda_2)$, infinitesimal homeostasis occurs at points where $Z_{\lambda_1} = Z_{\lambda_2} = 0$. Refer to Table 1 for a list of singularities of codimension ≤ 3. For each normal form, we ask whether the normal form has open regions of parameter space near the origin where the associated functions do not have infinitesimal homeostasis. This can be read off from the geometry described in [6, 8, 19], but it is easy to derive independently as follows.

For the cuspoids, which have the form $Z(\lambda_1, \lambda_2) = z(\lambda_1) \pm \lambda_2^2$, infinitesimal homeostasis occurs when $\lambda_2 = 0$ and $z'(\lambda_1) = 0$. Parameter values in the universal unfoldings of the cuspoids where infinitesimal homeostasis occurs are parameter values where $z'(\lambda_1) = 0$. Thus, perturbations of Morse functions and cusps always have infinitesimal homeostasis, whereas perturbations of folds and swallowtails have regions in unfolding parameter space that do not have infinitesimal homeostasis.

Infinitesimal homeostasis points for the hyperbolic umbilic satisfy

$$3\lambda_1^2 + a\lambda_2 + b = 0$$
$$3\lambda_2^2 + a\lambda_1 + c = 0.$$

If $a = 0$ and $b, c > 0$, then there are no infinitesimal homeostasis points. By continuity, there is an open set of parameter values (a, b, c) abutting on the origin without homeostasis points, as claimed.

Finally, infinitesimal homeostasis points for the elliptic umbilic satisfy

$$\begin{aligned} 3\lambda_1^2 - 3\lambda_2^2 + 2a\lambda_1 + b &= 0 \\ -6\lambda_1\lambda_2 + 2a\lambda_2 + c &= 0. \end{aligned} \tag{6.1}$$

It is shown in [19, pp. 180–184] that for every a, b, c near the origin, there is a solution λ_1, λ_2 of (6.1) near the origin. It follows that we can eliminate elliptic umbilics from our list. ∎

7. Comments about multiple outputs and networks. The study of input-output maps is much more difficult from a singularity theory point of view when the the number of outputs is greater than 1. The analog of (3.1) in Lemma 3.1 is

$$\tilde{Z}(\lambda) = \phi Z(\Lambda(\lambda)), \tag{7.1}$$

where $\Lambda : \mathbb{R}^k \to \mathbb{R}^k$ and $\phi : \mathbb{R}^\ell \to \mathbb{R}^\ell$ are diffeomorphisms. That is, the input-output function transforms by left-right (or $\mathcal{A}$) equivalence [8]. The associated singularity theory has been worked out in some dimensions (particularly $\ell = 2$ and $k = 1$ or $k = 2$).

As shown in [20], many manifestations of homeostasis occur in systems of equations that come from biochemical networks. In this context, the outputs are network nodes (which represent concentrations of chemical compounds). In this case, the natural collection of diffeomorphisms ϕ are those that preserve network structure [9]. For some networks—indeed, probably most—the permissible changes of coordinates reduce to (7.1). In others, the group of permissible ϕ is restricted, and the singularity theory in these cases has not been explored.

Finally, we note that network issues do not alter the set of relevant changes of coordinates when dealing with single-output homeostasis. So the issues discussed in this section do not affect the results of previous sections. A detailed discussion of multiple output homeostasis and the curious effects that networks might have on that topic is beyond the scope of this paper.

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